California State Journal of Medicine

OWNED AND PUBLISHED MONTHLY BY THE MEDICAL SOCIETY OF THE STATE OF CALIFORNIA

BUTLER BUILDING, 135 STOCKTON STREET, SAN FRANCISCO

Editor and Secretary - - - - - - - - - W. E. MUSGRAVE, M. D.
Associate Secretary - - - - - - - - HOWARD H. JOHNSON, M. D.
Managing Editor - - - - - - - - - CELESTINE J. SULLIVAN
Superintendent of Publications - - - - - - - - WILLIAM H. BARRY

VOL. XX AUGUST, 1922 No. 8

ORIGINAL ARTICLES

RESPONSIBILITY FOR STATEMENTS AND CONCLUSIONS IN ORIGINAL ARTICLES

The author of an article appearing in the JOURNAL is entirely responsible for all statements and conclusions. These may or may not be in harmony with the views of the editorial staff. Furthermore, authors are largely responsible for the language and method of presenting their subjects. All manuscripts will be carefully read, but editorial privileges will be exercised only to a very limited extent. It is believed that the manner of presentation of any subject by any author determines to no small degree the value of his conclusions. Therefore, both the author and the reader, in our opinion, are entitled to have the subject as presented by the author as little disturbed as possible by the editors. However, the right to reduce or reject any article is always reserved.

NON-DYSENTERIC AMEBIASIS *

By ALFRED C. REED, M. D., San Francisco.

The term "amebiasis" was coined in 1904 by Musgrave and Clegg in Manila to describe a "state of infection with amebas," and we are extremely fortunate here today in having with us in person one of the originators of this term, Dr. Musgrave, who has had the rare privilege of observing the development in this country and abroad of work stimulated and begun by himself twenty years ago. Man is subject to infection by at least five varieties of ameba. Of these we are convinced of pathogenicity in the case of one only—Entamœba histolytica. Kofoid and his colleagues have described as Councilmania lafleuri, a species of ameba which they believe to be pathogenic and to have been confused formerly with Entamœba coli. At present this species is under judgment, and its establishment as a new species is open to serious question, so that we can speak with unanimous authority of only one ameba, E. histolytica, whose pathogenic properties have been clearly demonstrated. This species alone, therefore, enters into the present discussion.

Amebiasis is widespread in the human race, some authorities estimating that as high as 10 per cent of the population of the globe is infected. An examination of 2300 overseas men and 576 home service men by Kofoid and Swezy led these workers to conclude that carriers of ameba in the United States were greatly increased by the return of the soldiers, and that carriers are more numerous than was expected among the normal population. Giffin, as early as 1913, in 1700 persons examined in the Middle Northwest, found 148 infected with E. coli, and 79 with E. histolytica.

In California there is evidence of a surprisingly high incidence, as indicated by numerous case reports and surveys. The sources of the endemic distribution in California are chiefly these:

1. Immigration from the Orient, especially of Filipinos, Chinese, Japanese, and East Indians.
2. Immigration and transient labor from Mexico.
3. Tourist travel from California to Asia.
4. The army demobilization.
5. Trade routes centering in California ports.

As in the case of other typically tropical diseases, so here, we have in California special problems and special dangers which require immediate attention.

While until recently considered predominantly a tropical affection, amebiasis is now known to be cosmopolitan and to invade practically every country of temperate climate as well as the tropics. There seems, however, to be a clinical difference in that dysentery is by far a more striking feature in the tropics than in higher latitudes. The common use of the term, tropical dysentery, as a synonym for amebic dysentery, is an illustration of this. It is important to keep clearly in mind that dysentery is merely a syndrome and not a specific disease. By dysentery we mean frequent bowel movements, containing blood and mucus and associated with pain and tenesmus. Dysentery is due to a large variety of causes of which ameba is only one.

An understanding of amebiasis from the clinical point of view requires an exact knowledge of its pathology and of the life cycle of the ameba. Under no circumstances are motile amebas in the dejecta infective for human beings. Their viability is too feeble and they probably never survive passage through the human stomach even if they get this far. Infection of man occurs solely through the agency of cysts. The vectors concerned in this transmission are chiefly water and flies. The cysts ingested by flies are found fully potent in their feces. Dependence on cyst-transference explains why amebiasis is invariably endemic and never epidemic in its incidence.

The cysts are ingested with food or drink by man and pass unchanged through the stomach. In the small intestine the cyst wall is dissolved and probably a single small quadri-nucleate ameba is released. This soon subdivides into four new

* From the Department of Medicine, Stanford University Medical School.

amebas which are carried by the intestinal flow to the colon.

Many authors have described invasion of the small intestine, but almost invariably the colon alone is attacked and the sites of election are the flexures, cecum and rectum. Dobell describes one method of invasion. In this the amebas are seen to congregate in large numbers on the surface of the healthy mucous membrane and gradually erode it by the secretion of a cytolytic ferment which dissolves the epithelial cells. The amebas soon lie in a pool of liquefied epithelium. Dobell states that they do not dislodge the epithelial cells mechanically or burrow between them. They do, however, according to this author, frequently invade the tissue through the crypts of Lieberkuhn. This is a stage of superficial erosion only and while the adjecent capillaries are dilated there is no true tissue reaction.

This erosion may develop into the characteristic type of amebic ulceration. The cytolytic action of the ameba here seen, gives the occasion for the name histolytica and is the one and only definite indication of the production by the ameba of an exotoxin. The ameba lives in direct contact with healthy tissues and not in the necrotic mass resulting from its activities.

Dobell describes the histologic picture as follows:

There first occurs a histolysis of the tissues in direct contact with the ameba and then a dilatation of the nearby capillaries with succeeding thrombosis and round-cell infiltration. Finally a necrosis of varying extent takes place. The typical amebic ulcer gives the appearance of a purely local lesion, with very little if any tissue reaction. The body tissues tend to regenerate whenever and wherever the amebas cease their activity or are removed by specific treatment. Some scar tissue is formed as well as new replacement tissues. The amebas are present in the lesions in vast numbers, in a large motile form. It is probably here that reproduction takes place by simple fission. A certain number of these large amebas, the ones destined for race propagation in a new host, leave the tissues and pass into the lumen of the colon where they are reduced in size and extrude all foreign material and food masses. Then as small, round, clear and very sluggish forms, they proceed to encyst by merely secreting a transparent thin coating. These cysts are carried out by the intestinal contents and their single nuclei subdivide twice, giving an ordinary maximum of four nuclei in the cysts seen in the stools.

Cyst production is not a constant activity of an ameba colony. It does not accur in amebic abscesses as in the liver or brain. Nor does it occur with any regularity in intestinal lesions. The biologic reasons for this are obscure but doubtless have to do with the lack of drainage of necrotic material, giving in general thereby an absence of any means for propagating an extension of the infection to a new host, and with the fact that the ameba under such conditions is not in an optimum environment for both forms of reproduction.

Under conditions favorable for its growth and reproduction, the ameba exists in a free-moving form, while under less favoring environment and when preparing for departure from its human host, it encysts in a resistant resting form. We have no evidence that under any circumstances E. histolytica can inhabit the human colon as a harmless commensal. As the infection increases in quantity and virulence, the clinical picture approaches that of dysentery. On the other hand, as the infection is less massive and vigorous, the clinical picture is that of non-dysenteric amebiasis, that is, of a carrier or chronic state. As various authorities have pointed out, granted an amebic infection, it is evident that this chronic or non-dysenteric state is the optimum both for parasite and for host. Non-dysenteric amebiasis is much more prevalent in temperate climates while dysentery and abscesses are more frequent in hot climates.

Several comments arise out of this survey of the pathology and life history.

1. All forms of amebiasis, in our present state of knowledge, pre-suppose and require that primary form of intestinal infection just described.

2. The ameba can invade the blood and lymph stream with the utmost ease. This is further proved by the occurrence of liver and brain abscesses. But thus far, no portal of entry has been proved except the one noted through the intestine.

3. While the ameba gives evidence of secreting a histolytic exotoxin, no other evidence of exotoxic action has been clearly demonstrated.

4. All clinical symptoms resulting from the presence of ameba in the body must be due to the following mechanisms:

(a) The effect of local pathologic changes in the intestine or other tissues directly invaded by the ameba.

(b) Absorption of amebic exotoxins of a more or less hypothetic nature.

(c) The absorption through amebic lesions of virtually parenteral protein or bacterial products. This latter is probably the explanation for the inflammatory reaction and enlargement of lymphatic glands draining regions of amebic invasion.

(d) Reflex effects resulting from the presence of amebas in the colon or elsewhere. If an inflamed appendix can be responsible for a reflex constipation, it is equally conceivable that an amebic lesion can cause intestinal and digestive disturbances through a reflex mechanism.

As seen in California, amebiasis in the great majority of cases is of the non-dysenteric type; that is, the infection exhibits an approximate balance between host and parasite and is apt to manifest itself in symptoms which are not a direct result of the lesion in the intestine. Almost any variety and degree of neurasthenia, physical depression, constipation, loss of weight, anemia, digestive troubles, vague aches and pains, and indefinite ill-health may be associated with amebiasis and disappear when the ameba is eliminated. In fact the symptoms may be so diverse, bizarre and unexpected that amebiasis is the last possibility to

be considered. This type of symptomatology is prevalent in California. In view of these considerations the following clinical rules may be drawn with conservatism:

1. Amebiasis is prevalent in California in non-dysenteric form.
2. Every patient suffering from gastro-intestinal symptoms should be investigated for the presence of ameba.
3. Every patient in whom the diagnosis is obscure or incomplete should be investigated for ameba.

Identification of ameba in the stools must include at least six consecutive daily specimens, including formed as well as fresh liquid stools, and must be conducted by a competent parasitologist.

Pathogenic amebas, that is, E. histolytica, have been described with certainty only in the intestine and in secondary abscesses as in the liver, lungs and brain. Reports of their occurrence elsewhere in the tissues of the body are subject to more or less criticism and are either inaccurate or premature at the present time. By many writers pathogenic amebas have been described in the urine and urinary bladder. Some few of these reports may be correct but the majority cannot be studied without the growing conviction that inflammatory or body tissue cells have been confused with amebas. We must recall that the leucocytes of normal blood have an ameboid motility and a cytology distinguishable with the utmost difficulty in fresh preparations from motile pathogenic amebas. This point was called to my attention by Herbert Gunn, who has been able to demonstrate the close similarity of fresh leucocytes with various wandering tissue cells, pus cells and amebas. Error is difficult to exclude. Always study of the free-moving forms must be amplified by identification of cysts when they occur, description of the nuclear structure and study of stained preparations before a valid opinion can be given. These criteria have not been met in the great majority of cases where amebas have been reported present in the urinary tract and elsewhere in the body outside the points of recognized incidence.

The same criteria may be brought with equal force against amebas reported in any tissue, as in the skin for instance. In the case of bile infections, a final word cannot be given. Gunn has had cases, one of which he has reported, where intestinal amebiasis cleared temporarily after removal of the gall bladder which apparently contained motile amebas. Permanent cure was prevented possibly by amebic infection in the bile ducts. It has been supposed that ameba would not live in the presence of bile so here, too, further light is needed.

There is little question that many persistent cases of amebiasis depend for their chronicity on an amebic focus in the appendix. It is probable that removal of the appendix would cure many such cases just as effectively and much more quickly than appendicostomy and colon irrigation through the stump. Skin infections have been described, partaking of the nature of a phagedena and associated with sinuses from a deep amebic abscess as in the liver. It is conceivable that amebas might infect cutaneous tissue by this method but the proof of it is not very definite.

The problem of the relations of ameba to the lesions of arthritis deformans, Ely's second great type of arthritis, has received considerable study in the past year at the Stanford Medical School. For several years claims have appeared in literature that ameba was related to this hypertrophic type of chronic osteo-arthritis. In 1906 Hunkin and Long, in San Francisco, attempted to show such a relationship. Since then John Barrow of Los Angeles has claimed that the relationship existed.

In the late summer of 1921 Barrow found E. histolytica in the stools of one of Ely's patients who suffered from hypertrophic arthritis of the spine. Relief or improvement not having followed the usual methods of treatment, this patient was given a course of specific amebic treatment with an immediate and remarkable clinical improvement. One relapse of arthritic symptoms was accompanied by a recurrence of cysts in the stools and the symptoms disappeared with a continuance of treatment. A second relapse was not accompanied by any evidence of intestinal amebiasis but improvement again followed resumption of amebic treatment, and has continued.

About this time Ely removed the head of a femur for this type of arthritis. Sections from the necrotic areas of this bone were stained with a standard iron hemotoxylin method and showed cellular bodies identified as E. histolytica. These bodies were abundant near the periphery of the necrosis and especially abundant around the capillaries. Their identification as amebas has not met with unanimous confirmation from those who have examined the sections. They were studied by Kofoid, who has already this afternoon detailed his conclusions about them. In an earlier note Kofoid and Swezy make the following statement:

"A portion of the head of a human femur, removed by operation in a case of arthritis deformans, reveals a pure infection of amebae about the characteristic lesions in the bone. No stained bacteria have been found in our examination. . . . The organisms interpreted by us as amebae are unlike known normal or pathologic tissue cells. They have the clear nuclear structure of Endamoeba dysenteriae (Councilman and Lafleur) found in tissues about amebic ulcers in intestinal amebiasis. Their nuclei are unlike those of endamoeba gingivalis."

Ely, Wyckoff and I have continued investigation of these lesions and have examined the stools in twenty cases of Type II arthritis in the clinic service. Of these only one showed histolytica. This patient was put on intensive treatment for amebiasis with the result or accompaniment that his arthritis became distinctly worse and remained worse. Cysts had not reappeared in his stools within two months after stopping treatment but physiotherapy had to be resumed to relieve his pain.

During the same period I saw seven other cases

of Type II arthritis. One only of these, the case already mentioned as the original in this series, harbored Entamoeba histolytica. One of these which had no evidence of amebiasis was put on moderately severe amebic treatment none the less and received immediate improvement which has lasted for some two months. I believe the explanation lies in the free elimination secured by the treatment and is along the line frequently noted of improvement following the use of colon irrigations and a diet designed to decrease putrefactive changes in the bowel. A second case was infected with an ameba which Kofoid diagnosed as Councilmania. The amebiasis was cured by specific emetin treatment and the clinical improvement was marked and has lasted some three months. Such a so-called therapeutic test as this seems to me worthless, however, as showing any relations between ameba and arthritis, for the same reason as stated above.

It is evident that bony changes in hypertrophic arthritis will outlast removal of the specific cause whatever that may prove to be, and it is more than possible that the symptoms of arthritis would persist likewise after removal of the specific cause. Effective treatment probably must be instituted in the early stages of the bone pathology and preferably on a preventive basis. Immediate improvement in the symptoms of arthritis after treatment with emetin preparations would in no sense argue for an amebic cause for the arthritis, but rather for immediate removal or subsidence of some focus of toxic absorption in the intestine. This is in line with mature clinical judgment.

Settlement of the present question of the causative relationship of the ameba will depend not on therapeutic experimentation but on demonstration of definite association histologically between ameba and bone lesion, and the experimental production specifically of such lesions.

It might be assumed that a comparison of the rate of incidence of ameba in Type II arthritis cases as compared with the rate of incidence at large would give conclusive evidence for or against the thesis that ameba is the cause of osteo-arthritis. But it is to be remembered that such statistics are at best only of inferential value and what value they possess is strictly proportioned to their quantity. Definite pathologic evidence alone would satisfy the requirements of the case.

This investigation is tedious and slow in its development and a considerable time will be required to affirm or disprove the suggestion that ameba is related to arthritis. Ely finds alveolar infection almost universal in Type II arthritis, yet the bone lesions seem without question to be non-bacterial in origin and, moreover, the E. gingivalis, so frequently associated with abscesses and granulomata in the dental area, has so far not been proved pathogenic. In a recent case of intestinal amebiasis, we examined the carious bone resected for the removal of deep dental infection. In the dental abscesses and granulomata E. gingivalis was abundant but no ameba-like cells of any sort were found within the bone itself. Nevertheless we are not yet prepared to state positively that the alveolar process can never be a portal of entry for pathogenic amebas.

Clinical experience thus far is too small to warrant statistical conclusions and for the purpose involved here, the importance of statistics is certainly minimal. We know that in other regions ameba may leave certain areas and move on or disappear, and the same factor doubtless would play a part if amebic bone infection were to occur.

There is, on the other hand, no evidence that amebiasis ever terminates spontaneously in the absence of specific treatment. Our personal impression is that the matter of bone invasion by ameba requires adequate investigation and that the suggestive data at hand amply justify further study. Lacking a bacterial cause for arthritis deformans, we can with logic seek a protozoal cause. Barrow believes that protozoan infection is present in 100 per cent of Type II arthritis. It will be necessary to demonstrate motile amebas in the fresh bone tissues, as cysts are not to be expected in such a location. As E. histolytica has not yet been successfully cultivated, experimental lesions are extremely difficult to secure at present.

While it is not certain that the intestinal tract is the sole portal of entry for pathogenic amebas, still thus far no other has been demonstrated. Treatment of intestinal amebiasis, therefore, might react favorably on a bone lesion in a non-specific manner by decreasing absorption of bacterial or protein products through intestinal ulcerations. The field of investigation is large and many unknown factors are doubtless involved. It is possible that a food deficiency analogous to a scorbutic deficiency may determine the bony localization of a protozoan parasite. We are convinced in any case that the inquiry must proceed along pathologic and experimental lines rather than in the hope of data from therapeutic or statistical methods in well-established cases of arthritis.

An unusual case of amebiasis was seen recently through the kindness of W. H. Barnes of San Francisco who reported it at the April meeting of the Stanford medical staff, and who intends to publish the detailed case report after longer observation.

A young woman, who had served as an army nurse, had suffered for five years from attacks of unusually severe asthma. During the same period she had recurring periods of diarrhea and sometimes of dysentery. No cause being found for the asthma, the stools were finally examined and E. histolytica was found in heavy infection. Specific treatment resulted in the temporary disappearance of the ameba and also in immediate relief of the asthma. Recurrence of ameba in the stools for a considerable period were concomitant with recurrences of severe asthma, which each time were relieved by specific treatment for amebiasis. Finally a more severe course of treatment was instituted with the hope of entirely eradicating the ameba, and in the course of the treatment she developed a severe arthritis. This is her status at present and Barnes' future report will record the end results.

Ordinarily asthma in the course of amebic infection is not affected by treatment for the latter.

The striking coincidence of the asthma and the intestinal symptoms and their common relief by specific amebic treatment are remarkable. The relation, if any, of the arthritis to the other conditions present has not yet been suggested.

In the treatment of amebiasis we believe that ipecac and its alkaloids alone are of value. Emetin hypodermically and bismuth emetin iodide by mouth are the only two preparations used, with the occasional addition of ipecac root. Neosalvarsan is added on the strong recommendation of Herbert Gunn who has found it to increase the efficiency of treatment. The bismuthous emetin iodide is given in powder form in gelatin capsules, three grains at night, if necessary preceded by opium. This drug is difficult to take and sometimes cannot be used in full dosage. Colon irrigations and oil enemas are used where there is evidence of marked colitis. Under like conditions the treatment is initiated by a short course of ipecac powder in massive doses. Other drugs are used solely for symptomatic indications, as for the benefit of digestion or the relief of colitis which may and often does outlast eradication of the ameba. Synthetic emetin is under trial at the suggestion of Barrow.

Treatment should be intensive and repeated milder courses administered in case of recurrence of cysts in the stools. Some cases have received definite benefit by resumption of mild treatment for purely symptomatic reasons when no cysts could be discovered. Alcresta ipecac is used at times for this purpose. It is mild in action, and much weaker than other ipecac preparations named, probably due to its admixture with kaolin.

The chief criterion of cure of amebiasis is the absence of cysts from the stools for a period of at least three months after termination of treatment. Examination for cysts, as already stated, requires at least six consecutive specimens on different days, including formed as well as fresh liquid movements.

In our investigations at the Stanford Medical School the stool examinations have been under the direction of Harry A. Wyckoff, clinical pathologist at Stanford Hospital.

(350 Post Street)

USING MEDICAL TERMS BEFORE PATIENTS

During the days when frock coats and whiskers were part of the physician's stock in trade, it was quite the custom for physicians to bewilder and frighten the patient by discussing his illness in Latin or in technical terms the patient could not understand. This custom should have disappeared with the frock coat, but it has not entirely done so.

The practice is and always was a deplorable example of poor taste, and now it is no longer legally safe. Many patients are sufficiently acquainted with the technical terms to understand, while others misunderstand and cause themselves worry and unhappiness.

In a number of court actions recently, physicians have been required to substantiate thoughtless statements made at the bedside, and it is likely that evidence of this kind will play a more and more important role in malpractice suits as time goes on.

A PLAN FOR THE INTENSIVE TREATMENT OF CONGENITAL SYPHILIS

PRELIMINARY REPORT

By HERMANN SCHUSSLER, JR., M. D., San Francisco.

The average physician, more particularly the general practitioner, has always considered the treatment of congenital syphilis as a most unsatisfactory part of his work. While many patients, especially young infants, show a strikingly clinical improvement under the influence of mercury alone, yet the Wassermann reaction is hardly ever made negative even when this drug is long and faithfully continued. The late case, with interstitial keratitis or a bone lesion, is generally looked upon as essentially incurable. Furthermore, many physicians feel that intensive arsenical therapy is either too difficult, too dangerous, or too painful to be used in infants and young children, except perhaps in the hands of one highly trained, and with all the facilities of the modern hospital at his disposal.

Recently Fordyce and Rosen, and Jeans have presented evidence that by following out in congenital syphilis a systematic plan of treatment similar to that used in adults, remarkable results can be obtained. Infants were apparently cured within a year, and most older children in two years. The methods described by these writers are not only efficient but safe, and simple enough to be carried out by anyone with medical training.

For the past two years we have been gradually improving, simplifying, and systematizing our routine plan of treatment for congenital syphilis at the Children's Clinic of Stanford University Medical School. Our aim has been to develop a method which the general practitioner can apply in the office or the home with a minimum of apparatus and trouble, with little or no discomfort or risk to the patient, and with the assurance that all the advantages of modern intensive anti-syphilitic therapy have been brought to bear upon the case. The method as it now stands may require further changes in the future, but we feel that the work has progressed far enough to justify this preliminary report.

General Plan of Treatment—When the Wassermann report comes back positive, the parents are carefully instructed as to the nature of the infection, the prognosis to the child with and without treatment, and the importance of regularity in attendance and of following out instructions to the letter. Wassermann tests are done on the parents and their other children, and the importance of treating the mother during future pregnancies is emphasized. The whole-hearted and faithful co-operation thus secured has contributed markedly to our good results.

If no contra-indication is found in the physical examination, the following course of treatment is begun at once:

1. Three intravenous injections of neoarsphenamine are given at 48-hour intervals.
2. Three mercurial inunctions are given every week for eight weeks.